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Role of estrogen in the acquisition of intravenously self-administered cocaine in female rats

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Abstract

Previous work from this laboratory has revealed that female rats acquired cocaine self-administration at a faster rate than male rats and that a greater percentage of females acquired self-administration [Psychopharmacology 144 (1999) 77.]. It has been suggested that sex differences in stimulant self-administration may be related to ovarian hormones, particularly estrogen. To investigate this possibility, we compared four groups ($n = 10$) of female rats: ovariectomized (OVX) treated with either estradiol benzoate (EB) or vehicle (VEH), and sham-operated intact (SH) females treated with either the antiestrogen tamoxifen (TAM) or VEH. An autoshaping procedure was used to train rats to lever press for intravenous infusions of cocaine (0.2 mg/kg). The criterion for cocaine acquisition was a mean of 100 self-administered infusions over five consecutive 6-h sessions. Results revealed that 70% of the OVX + EB group and 80% of the SH + VEH group acquired self-administration, while only 30% of the OVX + VEH group and 50% of the SH + TAM group met the acquisition criterion. Rats that had estrogen chemically or surgically blocked exhibited significantly less responding for cocaine over the acquisition testing period, and fewer of these rats met the acquisition criterion compared to intact rats and to OVX rats with estrogen (EB) replacement. The percentages for females with estrogen (70% and 80%) vs. those without (OVX, 30%) were similar to those reported for intact females (70%) and males (30%) in the previous study [Psychopharmacology (2000)]. Taken together, these results suggest that estrogen is a key factor influencing drug-seeking behavior in female rats, and it may underlie sex differences in drug-reinforced responding.

Keywords: Acquisition; Cocaine; Estradiol; Estrogen; Intravenous; Ovariectomy; Self-administration; Tamoxifen

1. Introduction

Factors that predict or alter the vulnerability to initiate drug self-administration have been the focus of numerous studies in recent years. Results from these studies identify a broad range of organismic, environmental, and physiological factors predictive of vulnerability (for review, see Carroll and Campbell, 2000). For example, sex is an important variable that is predictive of vulnerability during acquisition of drug self-administration (Lynch and Carroll, 1999). Specifically, female rats acquired cocaine self-administration at a faster rate than male rats, and a greater percentage of females (vs. males) acquired cocaine self-administration. The goal of this experiment was to examine the role of estrogen in the acquisition of drug self-administration.

Considerable evidence now suggests that ovarian hormones modulate both the behavioral effects and self-administration of stimulant drugs and thus may underlie sex differences during acquisition as well as during other phases of drug addiction (maintenance, reinstatement, and withdrawal). For example, self-administration of stimulants varies between males and females (Lynch and Carroll, 1999, 2000; Lynch et al., 2000; Roberts et al., 1989) and in females across different estrous cycle phases (Lynch et al., 2000; Roberts et al., 1989). During estrus, female rats responding for cocaine under a progressive ratio (PR) schedule reach break points considerably higher than those observed in males and during other phases of the estrous cycle (Roberts et al., 1989). Additionally, when responding for two concurrently available doses of cocaine, females in

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estrus respond almost exclusively for the highest cocaine dose available, whereas males and females in other phases do not show a preference for the highest dose (Lynch et al., 2000). Studies investigating the behavioral effects of stimulants reveal similar findings with females in estrus, displaying a greater response compared to males and females in other phases (Becker et al., 1982). These results are consistent with those showing that stimulant-induced dopamine (DA) release is enhanced during the estrus phase (Becker and Cha, 1989). Taken together, these results suggest that some component of the estrous cycle may affect stimulant self-administration in female rats.

Results obtained from ovariectomized (OVX) female rats suggest that estrogen in particular may play an important role in modulating the reinforcing and behavioral activating effects of stimulants. Specifically, ovariectomy abolishes sex differences in behavioral responses to stimulants, whereas castration does not affect the behavioral response (Camp et al., 1986). Moreover, estrogen replacement enhances behavioral sensitization in OVX rats to a similar degree to that observed in intact female rats (Peris et al., 1991; Sell et al., 2000). These results are consistent with those showing that estrogen can directly increase striatal DA release (Becker, 1990) and alter stimulant-induced DA release in the striatum (Becker, 1990; Becker and Ramirez, 1980; Castner et al., 1993).

The purpose of the present experiment was to investigate the role of estrogen in the acquisition of cocaine self-administration through the use of estrogen replacement in OVX female rats and tamoxifen (TAM; antiestrogen) in intact female rats. An automated autoshaping procedure was used that has previously been shown to be sensitive to differences in several factors such as drug dose, feeding condition, alternative reinforcers, and sex (Carroll and Lac, 1993, 1997, 1998; Lynch and Carroll, 1999). The autoshaping procedure has the advantage of standardized acquisition criteria that can be quantified and compared between groups. Based on findings that estrogen enhances behavioral responses to stimulants, we hypothesized that estrogen replacement in OVX females would facilitate acquisition, whereas ovariectomy and TAM treatment in intact females would impede acquisition compared to intact females. An additional goal of the present experiment was to compare percentage acquisition of cocaine self-administration obtained for each group in this experiment with that which has been recently published for intact female and male rats (Lynch and Carroll, 1999).

2. Method

2.1. Animals

Forty sexually mature, female Wistar (Harlan Sprague–Dawley) rats were housed individually in hanging stainless-steel home cages. Rats were approximately 90 days old and weighed 280–310 g at the beginning of the experiment. After a 5-day acclimation period, each rat was implanted with a chronic indwelling cannula and either OVX or sham OVX. Subsequently, the rats were placed in individual test chambers where they remained for the duration of the experiment. Rats had free access to ground Purina Laboratory Chow (Purina Mills, Minneapolis, MN) and water. Food and water were changed daily at 8:00 a.m. and intake of each was recorded. The experimental protocol was approved by the University of Minnesota Institutional Care and Use Committee under protocol number 9904A00343. Laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC), and Principles of Laboratory Animal Care (National Research Council, 1996) was followed.

2.2. Apparatus

Experimental test chambers were octagonally shaped with alternating Plexiglas and stainless-steel walls that contained an insertion for a drinking spout, a food jar, and two response levers (Coulbourn Instruments, Lehigh Valley, PA). Stimulus lights (4.76 W) were located 5 cm above each lever, and a house light (4.76 W) that was constantly illuminated was located at the top of the chamber. Each chamber was enclosed in a sound-attenuating wooden box that contained a fan for ventilation. An infusion pump (RHSYOCKC, Fluid Metering, Oyster Bay, NY) containing a 500-ml reservoir for the cocaine solution was mounted outside the chamber. Each reservoir was equipped with Tygon tubing (1.52 mm o.d.; 0.51 mm i.d.; Fisher Scientific, Springfield, NJ) that connected to a swivel (050-0022, Alice King Chatham, Hawthorne, CA) that was mounted at the top of the chamber. A tether (C313CS; Plastic Products, Roanoke, VA) was attached to the swivel and to the rat by a metal cannula (C3236; Plastics One, Roanoke, VA) that was embedded in the center of a plastic infusion harness (Instech Laboratories, Plymouth Meeting, PA). An IBM-compatible computer with Med–PC interface (Med Associates, St. Albans, VT) located in an adjacent room was used for programming and data collection and storage.

2.3. Drugs

Cocaine HCl was provided by the National Institute on Drug Abuse (Research Triangle Institute, Research Triangle Park, NC) and was mixed in sterile saline. Cocaine infusions (0.2 mg/kg) were delivered at a rate of 0.025 ml/s, and the infusion duration was 1 s/100 g of body weight. Cocaine solution was made weekly and stored in 500-ml reservoirs covered with aluminum foil outside each test chamber. TAM citrate, 17 β-estradiol benzoate (EB), and the peanut oil vehicle (VEH) were purchased from Sigma–Aldrich (St. Louis, MO). TAM (0.0024 g/ml) and EB (0.0006 g/ml) were dissolved in peanut oil and injected subcutaneously. This dosing procedure using 0.05 mg/kg for EB and 1 mg/

kg for TAM had previously been shown to reinstate sexual receptivity in OVX rats (Pfaus and Pfaff, 1992) and antagonize estrogen-dependent sexual behaviors (Arai and Gorski, 1968), respectively.

2.4. Procedure

Rats were anesthetized with a combination of ketamine (90 mg/kg) and pentobarbital (10 mg/kg). For the intravenous cannulation procedure, a silicon cannula was inserted into the right jugular vein of each rat following methods previously described (Carroll and Boe, 1982; Lynch et al., 2000; Weeks, 1972). The free tip was led subcutaneously to an incision 1 cm caudal to the scapulae and from there to an external harness (Instech, Plymouth Meeting, PA) and connected to a swivel at the top of the cage. Tygon tubing connected the swivel with the infusion pump. Ovariectomies and sham surgeries were performed via bilateral dorsal incisions the same day that the intravenous cannulas were implanted. Subjects were divided into four groups of 10 rats each: (1) OVX + EB, (2) OVX + VEH, (3) SH + TAM, or (4) SH + VEH. Five of the rats in the SH group did not have sham surgery. They were weight matched to the five that did, and their behavioral data did not differ from those that had sham surgery. They were included in the group of 10. Beginning 3 days after surgery, rats were given daily injections (subcutaneously) at 8:30 a.m. of EB (0.05 mg/kg), TAM (1.0 mg/kg), or an equal volume of VEH. Since estrogen had previously been shown to affect feeding behavior (Tarttelin and Gorski, 1973), self-administration sessions began 7 days after the first pretreatment to allow food intake to stabilize.

The autoshaping program that was used has been previously reported (Carroll and Lac, 1993, 1997, 1998; Lynch and Carroll, 1999). Daily autoshaping sessions began at 9:00 a.m. and consisted of six 1-h autoshaping components followed by a 6-h self-administration component. At the beginning of each session, three stimulus lights above the retractable lever and the inactive lever were illuminated. During each of the six 1-h autoshaping components, the retractable lever was extended 10 times into the test chamber on a random interval schedule with a mean of 90 s. The lever was retracted when the rat pressed the lever or after 15 s, whichever occurred first. A cocaine infusion was delivered 1 s after each lever retraction. Lever presses on the inactive lever were counted but were not reinforced. After the 10 infusions were delivered, there was a timeout for the remainder of the hour, and the lever remained retracted, stimulus lights were off, and responding had no programmed consequences.

These six 1-h autoshaping components were followed by a 6-h self-administration component. During this period, the lever remained extended and the lights above the levers were illuminated every time an infusion occurred. Each lever press *on the active lever* resulted in an infusion of cocaine. A timeout occurred at the end of the 6-h self-administration session and all stimulus lights were extinguished. The criterion for acquisition of cocaine self-administration was a mean of 100 or more infusions during the self-administration component over five consecutive sessions. This acquisition criterion was based on previous research conducted in this laboratory (Carroll and Lac, 1993, 1997, 1998; Lynch and Carroll, 1999). The criterion of 5 days was designed to capture the entire acquisition process. Acquisition of cocaine self-administration is characterized by initial low levels of responding (Days 1–2), followed by a peak in responding (Day 3), and then responding stabilizes at a maximum level. Thus, the average of 100 infusions required for the criterion to be met is actually about half the number of infusions taken once the animals stabilize at high rates. If this criterion was not met within 30 days of the first autoshaping session, the experiment was terminated. Body weights were recorded weekly and cannula patency was assessed approximately every 7 days by an injection of sodium methohexital (5.0 mg/kg). Patency was assumed if loss of muscle tone was observed immediately after the injection. If a cannula was not patent, a new one was implanted into the left jugular vein and testing resumed 3 days after surgery.

To obtain information regarding the estrous cycle, rats were vaginally swabbed daily at 2:30 p.m. Swabbing began 7 days before self-administration training to acclimate rats to the procedure. Vaginal swabs were placed on slides, stained with methylene blue, cover slipped, and examined under light microscopy. Metestrus and diestrus were categorized together and were characterized by few cells, the presence of leukocytes, and necrotic epithelia. Proestrus and estrus were categorized separately and were characterized by the presence of predominantly nucleated epithelial cells and predominantly nonnucleated cornified epithelial cells, respectively.

2.5. Data analysis

Dependent measures were number of days to meet the acquisition criterion, the percentage of rats per group to meet acquisition criterion, drug intake during the last five self-administration sessions, and food intake. Data from five intact female rats used in the Lynch and Carroll (1999) cocaine acquisition study were included in the SH + VEH group. Subjects were exposed to the same acquisition procedure they received the same dose of cocaine, and they were matched by body weight to those in the present study. Although these rats were tested at a different time than the rats in the present study, statistical analyses showed no significant differences between body weights, mean food or water intake, or mean number of cocaine infusions over the entire acquisition period. Based on the hypothesis that estrogen is a key factor modulating the reinforcing effects of cocaine during acquisition, four separate comparisons were examined: (1) SH + VEH vs. OVX + VEH, (2)

SH + TAM vs. SH + VEH, (3) OVX + VEH vs. OVX + EB, and (4) OVX + EB vs. SH + VEH. Separate one-tailed *t* tests were used for all predicted a priori comparisons, and separate two-tailed *t* tests were used for all other a priori comparisons. The Kaplan–Meier survival analysis (GB-Stat School Pak; Dynamic Microsystems, Silver Spring, MD) and the log rank test were used to compare survival functions between groups.

3. Results

Fig. 1 represents the percentage of rats from each group that met the acquisition criterion for cocaine self-administration. Percentage acquisition for each group was 80% for the SH + VEH rats, 30% for the OVX + VEH rats, 50% for the SH + TAM rats, and 70% for the OVX + EB rats. The acquisition criterion was met in a mean of 11.7 ± 3.25, 22.5 ± 3.82, 21.8 ± 3.63, and 15.5 ± 3.41 days for the SH + VEH, OVX + VEH, SH + TAM, and OVX + EB groups, respectively. Survival analyses were used to test for differences in percentage acquisition between each group. The results, which produced the log rank statistics, revealed significant differences between the SH + VEH and the OVX + VEH groups ($c^2 = 4.377$, $df = 1$, $P < .05$) and the SH + TAM and the SH + VEH groups ($c^2 = 3.694$, $df = 1$, $P < .05$) but only a marginal difference between the OVX + EB and the OVX + VEH groups ($c^2 = 3.694$, $df = 1$, $P = .06$). This latter finding can be attributed to the fact that each of the three rats that met the acquisition criterion in the OVX + VEH did so within the first 5 days of testing. An analysis comparing all of the rats in both groups (i.e. those that acquired and those that did not) on total cocaine infusions over the last 5 acquisition testing days revealed that rats in the OVX + EB group self-administered significantly more cocaine compared to rats in the OVX + VEH group ($t = 1.876$, $df = 18$, $P < .05$). Additionally, no significant differences were observed between the OVX + EB and the SH + VEH groups on percentage acquisition. Therefore, rats that had estrogen chemically or surgically blocked exhibited significantly less responding for cocaine over the acquisition testing period, and fewer of these rats met the acquisition criterion compared to intact rats and to OVX rats with estrogen (EB) replacement.

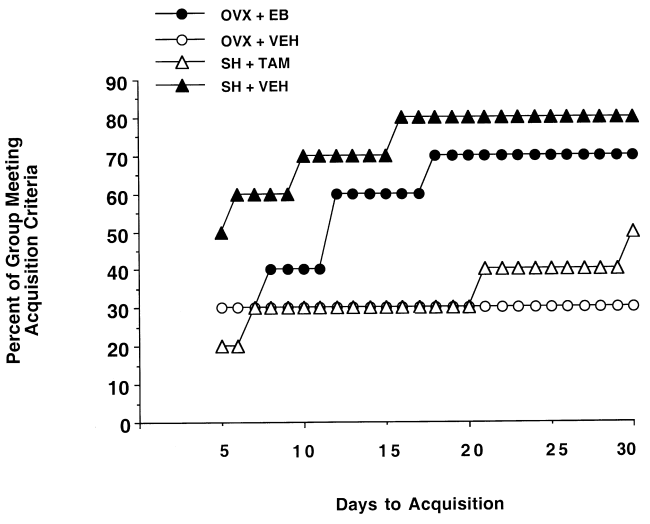

Fig. 1. The percentage of each group of rats that met the cocaine (0.2 mg/kg) acquisition criterion (a mean of ≥100 infusions over 5 consecutive days) within the 30-day limit. Data are presented as a function of day during the autoshaping testing period. The percentages of SH + VEH rats (filled triangles) and OVX + EB rats (filled circles) that acquired were significantly greater than the OVX + VEH (open circles).

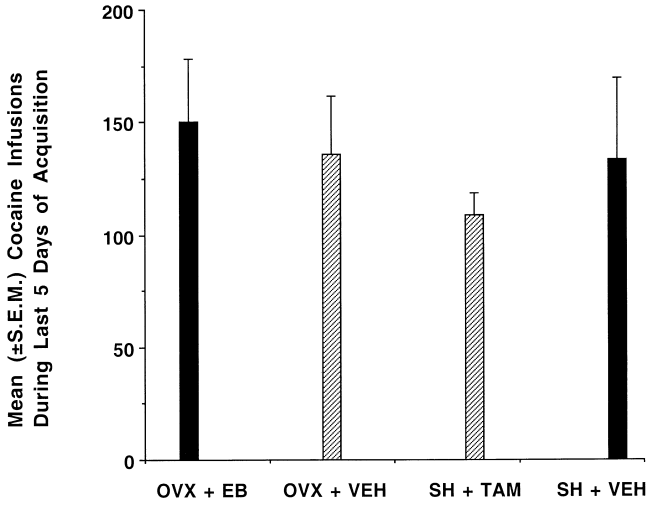

Fig. 2. Mean ± S.E.M. number of cocaine (0.2 mg/kg) infusions for each group of rats is presented for the last 5 days of acquisition when the criterion for acquisition was met. Bars are shaded black to indicate the presence of estrogen, and gray refers to the absence of estrogen.

In Fig. 2, mean number of cocaine infusions per day across the last 5 days of the acquisition procedure are presented for the rats that acquired drug self-administration in each group. Mean drug intake was slightly greater in the groups with estrogen (OVX + EB and SH + VEH) compared to the groups that did not have estrogen (OVX + VEH and SH + TAM); however, these differences did not reach statistical significance. The number of inactive lever responses during the 6-h self-administration sessions was low throughout the acquisition testing period, and they did not differ significantly between groups. Between-group comparisons revealed no significant differences regarding food or water intake (data not shown).

Slides obtained from vaginal swabs confirmed hormonal status for each of the four treatment groups. Specifically, proestrus-like cells predominated vaginal smears obtained from the OVX + EB group, while vaginal smears obtained from rats in the SH + VEH group demonstrated normal three to five cycles. Metestrus- and diestrus-like cells predominated vaginal smears obtained from both the OVX + VEH and the SH + TAM groups.

4. Discussion

The results of the present experiment revealed that acquisition of cocaine self-administration was markedly reduced by ovariectomy (30%) and restored by estrogen replacement (70%). Additionally, the percentages of SH + VEH (80%) and OVX + VEH (30%) females that met the acquisition criterion in the present experiment were analogous to those reported in earlier work for intact female (70%) and male rats (30%), respectively (Lynch and Carroll, 1999). These findings are consistent with previous research showing that females are more sensitive than males to the behavioral activating effects of acute injections of stimulants (Becker et al., 1982; Diaz-Veliz et al., 1994; Glick and Hinds, 1994; Haney et al., 1995; Robinson, 1984; Schneider and Norton, 1979; Sell et al., 2000), that ovariectomy abolishes this sex difference (Camp et al., 1986; Sell et al., 2000), and that estrogen replacement restores this sex difference (Peris et al., 1991; Sell et al., 2000).

The present finding that estrogen replacement in OVX females increased percentage acquisition to a level similar to that observed in intact females is consistent with the hypothesis that estrogen is a key factor influencing the reinforcing effects of cocaine in female rats. One possible mechanism underlying estradiol's effect on acquisition of cocaine self-administration is through its interaction with DA. Specifically, the mesolimbic DA system is believed to mediate the reinforcing value of cocaine. Previous research has shown that DA release and reuptake in this area fluctuate over the estrous cycle (Shimizu and Bray, 1993), and that EB modifies DA activity in OVX females (Shimizu and Bray, 1993), alters stimulant-induced DA release in the striatum (Peris et al., 1991), and can directly modulate DA release in the striatum (Becker, 1990). In the present experiment, the goal was to determine the effect of estrogen levels that are similar to those observed during proestrus/estrus cycles. Although the dose of EB tested was within a physiological range, it should be noted that a normal rat is not exposed to this level of estrogen for a prolonged period of time.

The present finding that estrogen replacement in OVX females increased percentage acquisition is in contrast to results obtained previously with females self-administering cocaine during a maintenance phase. Specifically, Grimm and See (1997) investigated the effect of estrogen replacement in OVX females responding under a PR schedule, and they found that chronic estrogen treatment had no effect on responding. The discrepancy between the results of the present experiment and those reported in this previous experiment for chronic estrogen replacement may be due to differences in the dosing protocols used. Specifically, in the present experiment, subcutaneous injections of EB were administered daily, whereas in the previous experiment, capsules containing EB were implanted subcutaneously, resulting in a more steady release of estrogen. Although not specifically investigated, previous research conducted on the effect of acute and chronic estrogen treatment suggests that dosing schedule may determine the drug effect. For example, acute estrogen treatment resulted in a rapid increase (within 30 min) in stimulant-induced striatal DA release and potentiated stimulant-induced behaviors, whereas chronic treatment resulted in a decrease in dopaminergic activity and increased D_2 DA receptor sensitivity (Becker, 1999; Hruska and Silbergeld, 1980; Nausieda et al., 1979). Thus, different dosing conditions may produce very different changes in dopaminergic activity and behavior. However, the effects of prolonged steady state levels of EB and daily elevated levels of EB on dopaminergic activity are not known.

Pharmacological blockade of estrogen via TAM significantly reduced acquisition of cocaine self-administration in intact females. This result is consistent with previous research showing that TAM attenuates haloperidol's (DA agonist) augmentation of cocaine self-administration in intact female rats (Dalton et al., 1986). The mechanism underlying TAM's effect of cocaine self-administration is not clear. While TAM exerts direct effects on estrogen receptors, results from an in vitro superfusion experiment revealed that it was not effective at blocking the enhancing effects of estrogen on amphetamine-induced striatal DA release (Xiao and Becker, 1997). Thus, TAM may not be antiestrogenic at all receptors. However, when TAM is tested for an extended period of time, as in the present experiment, it has been shown to antagonize estrogen-induced striatal DA receptor sensitivity (Glick and Hinds, 1994).

Understanding the factors that affect cocaine self-administration in the female rat may yield valuable strategies for cocaine abuse prevention and treatment in women. Although the rat estrous cycle can not be compared to the human menstrual cycle, these results reveal that the female sex hormone, estrogen, can influence the reinforcing effects of cocaine. These results, combined with previous findings that estrogen can directly influence dopaminergic transmission, may have important clinical implications.

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